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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,388	11/21/2001	Wataru Morikawa	MORIKAWA4A	1349

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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,388	MORIKAWA ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7/15/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments and Amendments

1. Claims 1-4 are pending.

Claims 1-4 have been amended.

Claims 1-4 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. The information disclosure statement filed July 15, 2003 has not been considered in its entirety. There are several references that did not accompany the file. These references are AD, AH, AK, AM, and AO and the information referred to therein has not been considered as to the merits and have been "lined through". The listings have been lined through and Applicants are invited to resubmit these documents.

Withdrawn Objection

Specification

4 The disclosure is no longer objected to because the specification has been amended to correct misspelled words and other typographical errors.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

5. The rejection of claim 4 is under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition for inhibiting lung tumor metastasis and lung tumor growth, does not reasonably provide enablement for a composition for inhibiting any and all tumor metastasis and any and all tumor growth is withdrawn in light of the claim amendment.

6. The rejection of claims 1-4 under 35 U.S.C. 112, second paragraph, set forth in Paper 5, mailed July 15, 2003 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the claim amendment and Applicant's arguments.

Maintained and New Grounds of Rejection

Claim Rejections - 35 USC § 112

7. The rejection of claims 1-4 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claim(s) continue to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants assert that the claims have been amended to limit the plasminogen to human plasminogen. The Examiner has reviewed the claims and considered this assertion and found that this point of view is partially persuasive.

All of the claims have not been sufficiently amended in order to obviate the instant rejection. The naturally occurring plasminogen of claims 1and 2 reads on any and all plasminogen from any species. Applicants have provided support only for the preparation of a human plasminogen fragment. The rejection is maintained for the reasons set forth and of record.

Claim Rejections - 35 USC § 112

8. Claims 1 is under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition for inhibiting lung tumor metastasis and lung tumor growth, does not reasonably provide enablement for a composition for inhibiting any and all tumor metastasis and any and all tumor growth is withdrawn in light of the claim amendment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants have set forth data that supports the inhibition of lung cancer metastasis and growth, as well as the inhibitory effects of fractions with heparin binding activity on lung tumor metastasis and growth, see Examples 7, 8 and 9, pages 21-23 corresponding to Figure 7 and 8; Example 10, page 24 corresponding to Figure 9. However, the breadth of the claims encompasses the broad treatment of tumor

metastasis and tumor growth and the specification is insufficient to enable one of skill in the art to practice the invention absent an undue amount of experimentation. Some of the considerations in determining what constitutes undue experimentation have been summarized as follows: (1) the amount of direction or guidance presented; (2) the presence or absence of working examples; (3) the breadth of the claims; (4) the state of the prior art; (5) the predictability or unpredictability of the art. *Ex parte Formal, et al.*, 230 USPQ 546 (BPAI, 1986).

As set forth in IDS document, AG the potential for using agents, such as cytokines and antibodies in cancer therapy is great, but clinical results to date have not met the high expectation extrapolated from carefully planned and performed preclinical studies, see bridging paragraph of pages 1079 and 1080. Well-established cancer agents must overcome the physiological barriers to penetrate tumor tissue, effective in *in vivo* microenvironment of solid tumors and reach the target cells *in vivo* in effective quantities with minimal toxicity to normal tissues, see first full paragraph of column 1, page 1080. Applicants claimed cancer agents has not established a sufficient precedent in treatment of a variety of tumors. Applicants have provided data that supports the administration of an effective dose of Lys-LBS-I to immunodeficient mice, however one cannot extrapolate the results based upon one type of tumor to all tumor types. "Even with the best animal model, however, we still need to better understand how the process of biodistribution of various agents "scales-up" from mouse to human.", see column 2 on page 1080.

The selection and development of such therapeutics is art known to be highly unpredictable. The specification exemplifies no examples of the effective use of any composition consisting of Kringles 1 to Kringle 3 of a naturally occurring plasminogen other than the human Lys-LBS I fragment of human plasminogen as a therapeutic pharmacological agent. Therefore, due to the unpredictability of therapeutics and the absence of any evidence concerning the effectiveness of the broadly claimed composition as a pharmacological agent, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use with a reasonable expectation of success, the invention commensurate in scope with this claim. Additionally, it would require undue experimentation of one skilled in the art to apply a method of treatment to a human based on the teachings of a method of treating a non-human animal.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is vague and indefinite in the recitation "binds less intensely". It is not clear what is deemed intense, how that intensity is measured and what molecules the comparison is based upon. Accordingly, the metes and bounds cannot be determined.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent number 5,288,489 (February 22, 1994/ IDS reference AA). U.S. Patent #5,288,489 discloses a Lys-Lys binding site I which is a plasminogen fragment consisting of Kringle 1 to Kringle 3 which is derived from glu-plasminogen by limited proteolysis, catalyzed by plasmin, whereby a peptide fragment is cleaved fro the amino terminal domain, see column 8, lines 45-65. "[T]he glu-plasminogen is the naturally occurring form of plasminogen", see column 8, lines 45 and 46. The patent also discloses that the mini-plasminogen is derived form either glu- or lys-plasminogen catalyzed by pancreatic elastase, see column 8, lines 52-58.

Although patent '489 does not specifically recite the molecular weight, lack of glycosylation, heparin binding activity and inhibiting tumor metastasis and tumor growth these limitations would be inherent qualities of the recovered compound (which encompasses the Lys-Lysine binding site I), especially in light of the fact that the method of the patent and the method of the instant application are the same.

13. Claims 1-4 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 5,801,146 (filed May 3, 1996/ IDS reference AC). U.S. Patent number

5,801,146 discloses a compound and method for inhibiting angiogenesis, a process depended upon for growth and metastasis of tumors, see column 1, lines 43-46. The patent discloses a Lys-Lys binding site I which is a plasminogen fragment consisting of Kringle 1 to Kringle 3 which is derived from glu-plasminogen by limited proteolysis, catalyzed by plasmin, whereby a peptide fragment is cleaved fro the amino terminal domain, see column 4, lines 46-57. The Lys-plasminogen is a naturally truncated form of plasminogen. The patent also discloses that the mini-plasminogen arises form elastase digestion of lys-plasminogen, see column 4, lines 53-57.

Although patent '146 does not specifically recite the molecular weight, lack of glycosylation, heparin binding activity and inhibiting tumor metastasis and tumor growth these limitations would be inherent qualities of the recovered compound (which encompasses the Lys-Lysine binding site I), especially in light of the fact that the method of the patent and the method of the instant application are the same.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 7:00 am to 4:30 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4315.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
12 January 2004